Tamsulosin HCl

Prozelax®

200 mcg Sustained Release Capsule

Alpha$_1$- Adrenoreceptor Antagonist

FORMULATIONS

Each capsule contains:

Tamsulosin hydrochloride (sustained release microgranules)..... 200 mcg

PRODUCT DESCRIPTION

Tamsulosin (Prozelax®) 200 mcg capsule: white to off-white pellets in a capsule with a slightly pink cap and off white body

PHARMACOLOGY

Pharmacodynamics
Tamsulosin HCl is a sulfamoylphenethylamine derivative alpha$_1$-adrenergic blocking agent (alpha$_1$-adrenoceptor antagonist). It binds selectively and competitively to postsynaptic alpha$_1$-adrenoceptors, in particular to subtypes alpha$_{1L}$ and alpha$_{1A}$. About 70% of alpha$_1$-receptors in human prostate are of the alpha$_{1A}$ subtype. Tamsulosin brings about relaxation of prostatic and urethral smooth muscles resulting in improved urinary flow rate and a reduction in symptoms of benign prostatic hyperplasia (BPH). It also improves the irritative symptoms in which bladder instability plays an important role.

Tamsulosin's ability to decrease intra-ureteral pressure and increase fluid passage has also been shown to be effective in medical expulsive therapy in increasing the rate of spontaneous stone passage.

Alpha$_1$-blockers can reduce blood pressure by lowering peripheral resistance. Selectivity of tamsulosin for alpha$_{1A}$-receptors which are mainly located in nonvascular smooth muscle (e.g., prostate) may result in a reduced incidence of adverse cardiovascular effects (e.g., syncope, dizziness, hypotension).

Pharmacokinetics
The plasma levels of tamsulosin HCl gradually increases reaching peak concentrations (Cmax) at a median time of 6 hours after a single dose of tamsulosin 400 mcg extended release in the fasted state. At steady state (reached by day 4 of multiple dosing), plasma concentrations of tamsulosin peak at 4 to 6 hours under fasting and fed conditions. An increase in peak plasma concentrations is observed from approximately 6 ng/mL after the first dose to 11 ng/mL in steady state. The plasma concentration decreases after the Cmax is reached; however, at approximately 16 to 24 hours post-dose, a small increase or second plateau is observed. The absolute bioavailability of tamsulosin is estimated to be 55 to 59%. Absorption of tamsulosin is reduced by a recent meal.

Tamsulosin's mean steady-state apparent volume of distribution after intravenous (IV) administration is 16 L, which suggests distribution into extracellular fluids.

Tamsulosin is 94 to 99% bound to plasma proteins primarily alpha$_1$ acid glycoproteins. It is extensively metabolized by cytochrome P450 enzymes (CYP3A4 and CYP2D6 isoenzymes) in the liver; less than 10% of the dose is excreted in the urine unchanged. The metabolites of tamsulosin undergo extensive conjugation to glucuronide or sulfate prior to renal excretion. Tamsulosin's pharmacokinetic profile in humans has not been fully established, thus, possible interactions with other cytochrome P450 metabolized compounds cannot be predicted.

Tamsulosin is primarily excreted through the urine with approximately 9% of the dose excreted as unchanged drug. Because of the absorption rate-controlled pharmacokinetics of tamsulosin capsule, the apparent half-life of tamsulosin increases to about 12 to 15 hours in healthy volunteers.

INDICATIONS

Treatment of the signs and symptoms of benign prostatic hyperplasia/hypertrophy (BPH) including bladder outlet obstruction

DOSAGE AND ADMINISTRATION

Swallow capsule whole. Do not open, chew or crush.
Note: Tamsulosin sustained-release pellets are packed in hard capsules. (Changes in Pharmacokinetics may occur if the granules are taken without the enclosing capsule)

Usual Adult Dose:
Orally, 200mcg (1 capsule) once daily, preferably without food.
Or, as prescribed by a physician.

CONTRAINDICATIONS

Hypersensitivity to tamsulosin hydrochloride or to any component of the product.
A history of orthostatic hypotension
Severe hepatic insufficiency

WARNINGS AND PRECAUTIONS

As with all alpha$_1$-adrenoceptor antagonists, blood pressure reduction can occur in patients receiving tamsulosin which rarely may result in syncope. At the first signs of orthostatic hypotension (dizziness, weakness), patient should be advised to sit or lie down until the symptoms have disappeared.

Caution patients starting tamsulosin treatment to avoid situations where injury could result should syncope occur.

Orthostastic Hypotension
Syncope is the most severe orthostatic symptom of α_1-adrenoceptor antagonists. Other symptoms such as postural hypotension, dizziness and vertigo can also occur.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with caution. Patients who experience hypotension should be placed in the supine position. If still inadequate, volume expansion with IV fluids or vasopressor therapy may be applies. A transient hypotensive response is not a contraindication to further therapy with tamsulosin.

Prostate Cancer
Carcinoma of the prostate and BPH have similar symptoms and these two diseases frequently co-exist. Evaluate patients prior to starting tamsulosin treatment and at regular intervals afterwards to rule out the presence of carcinoma of the prostate. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed.

Priapism and Ejaculation Disorders
Tamsulosin, like other alpha$_1$-blockers, has been rarely (probably less than one in 50,000 patients) associated with priapism (persistent painful penile erection unrelated to sexual activity). This condition could lead to impotence if not properly treated. Patients must be advised about the seriousness of this condition.

Ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported with the use of tamsulosin.

Intraoperative Floppy Iris Syndrome (IFIS)
During post-marketing surveillance, IFIS has been observed during cataract and glaucoma surgery in some patients treated with alpha$_1$-blockers including tamsulosin. Most reports were in patients taking the alpha$_1$-blocker when IFIS occurred. However, some cases occurred even after the alpha$_1$-blocker has been discontinued before surgery.

IFIS, a variant of small pupil syndrome, manifests as a combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis even with preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications of their surgical technique such as utilization of iris hooks, iris dilator rings or viscoelastic substances. The benefits of stopping alpha$_1$-blocker therapy before cataract surgery have not been established.

The risk of eye complications during and after the operation is increased by IFIS. The benefit of stopping alpha blocker therapy before cataract or glaucoma surgery has not been established. The initiation of tamsulosin is not recommended in patients who is scheduled for cataract or glaucoma surgery.

Sulfa Allergy
Allergic reactions with tamsulosin HCl have been rarely reported in patients with sulfa allergy. Administer tamsulosin HCl with caution in patients who have serious or life threatening sulfa allergy.

Effects on Ability to Drive or Use Machines
Although there are no specific studies conducted on tamsulosin and the ability to drive vehicles or use machines, tamsulosin may cause dizziness. Patients receiving tamsulosin should be advised to take precautions while performing activities requiring mental alertness or physical coordination. It should be carefully considered whether it is advisable to drive or operate machinery under these circumstances.

INTERACTION WITH OTHER MEDICAMENTS

Cytochrome P450 Inhibition
Strong and Moderate Inhibitors of CYP3A4 or CYP2D6: Tamsulosin is extensively and mainly metabolized by CYP3A4 and CYP2D6 isoenzymes.

Concomitant administration of ketoconazole, a strong inhibitor of CYP3A4 isoenzyme, may increase the Cmax and AUC of tamsulosin by a factor of 2.2 and 2.8, respectively. Combined use is not recommended.

The effect of concomitant administration of moderate inhibitors of CYP3A4 (e.g., erythromycin) on the pharmacokinetics of tamsulosin have not been studied.

Concomitant administration of paroxetine, a strong inhibitor of CYP2D6 isoenzyme, may increase the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively. Similarly, an increase in exposure was identified in poor metabolizers of CYP2D6 compared to extensive metabolizers of CYP2D6. Since CYP2D6 poor metabolizers cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin is co-administered with strong CYP3A4 inhibitors in these patients, the use of strong CYP3A4 inhibitors in CYP2D6 poor metabolizers are not recommended.

The effect of concomitant administration of moderate inhibitors of CYP2D6 (e.g., terbinafine) on the pharmacokinetics of tamsulosin have not been evaluated.

Concomitant administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin has not been evaluated. A potential significant increase in tamsulosin exposure, however, is expected when tamsulosin is administered with a combination of strong inhibitors of both CYP3A4 and CYP2D6.

Alpha-adrenergic Blocking Agents: Pharmacokinetic and pharmacodynamic interactions between tamsulosin and other alpha-adrenergic blocking agents have not been determined. Do not use tamsulosin in combination with these agents since interactions may be expected.

PDE5 Inhibitors: Concomitant administration of alpha-adrenergic blocking agents and PDE5 inhibitors may lower blood pressure and cause hypotension due to their vasodilating effects. Caution is advised when these drugs are given concomitantly.

Warfarin: Warfarin may increase the elimination rate of tamsulosin *in vitro*. Exercise caution when tamsulosin is administered concomitantly with warfarin.

Nifedipine, Atenolol, Enalapril: There is no clinically significant effects on blood pressure and pulse rate when nifedipine, atenolol or enalapril are taken together with tamsulosin. Concomitant administration with tamsulosin requires no dosage adjustment.

Digoxin and Theophylline: Orally administered tamsulosin taken concomitantly with digoxin and theophylline resulted in no change in the pharmacokinetics of digoxin or theophylline. No dosage adjustments are necessary when these drugs are taken concomitantly.

Furosemide: Orally administered tamsulosin taken concomitantly with furosemide 20 mg single IV dose had no effect on the pharmacodynamics of furosemide. Although furosemide reduced the maximum concentration (Cmax) and AUC of tamsulosin, dosage adjustment is not required since these changes are expected to be clinically insignificant.

Cimetidine: Tamsulosin's clearance was significantly decreased by 26% which resulted in a moderate increase in AUC (44%) with concomitant treatment with cimetidine. Use tamsulosin with caution when used in combination with cimetidine.

Other in vitro findings:
Diazepam, propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin, salbutamol, finasteride, and warfarin did not change the free fraction of tamsulosin in human plasma *in vitro*.

Laboratory Findings:
There are no known laboratory test interactions with the use of tamsulosin. Tamsulosin treatment for up to 3 months has been shown to have no significant effect on prostate specific antigen (PSA).

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy and Lactation
Pregnancy Category B
There is no adequate data on the use of tamsulosin HCl in pregnant and breastfeeding women. The potential risk from the use of tamsulosin during pregnancy and breastfeeding in humans is unknown.

Infants and Children
Tamsulosin HCl is not indicated for use in children.

Elderly
No substantial differences in safety and efficacy have been demonstrated relative to younger adults, but increased sensitivity cannot be ruled out.

Hepatic and Renal Impairment
Use with caution in patients with hepatic or renal impairment since there are no studies on the effects of tamsulosin in these populations.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Body as a Whole: Headache, infection (including cold, common cold, flu, and flu–like symptoms), asthenia, pain, back pain, chest pain, abdominal pain, accidental injury, flu syndrome, neck pain, fever, chills, malaise, fatigue.

Cardiovascular Effects: Hypertension, palpitations, hypotension, postural hypotension, tachycardia, atrial fibrillation, arrhythmia,
There is a potential risk of syncope in tamsulosin treated patients. *(see **Warnings and Precautions**)*

Gastrointestinal Effects: Diarrhea, dyspepsia, vomiting, nausea, constipation, dry mouth, tooth disorder.

Metabolic and Nutritional Effects: Peripheral edema.

Musculoskeletal Effects: Arthralgia, myalgia, arthritis.

CNS Effects: Dizziness, dizziness (aggravated), dizzy spell, vertigo, syncope, orthostatic/circulatory collapse, somnolence, insomnia, depressed level/loss of consciousness, hypertonia, paresthesia.

Respiratory Effects: Rhinitis (including nasal congestion, nasal obstruction, stuffy nose, runny nose, sinus congestion, and hay fever), pharyngitis, increased cough, sinusitis, dyspnea, lung disorder, epistaxis

Dermatologic Effects: Allergic type reactions such as skin rash, urticaria, pruritus, angioedema and respiratory symptoms, skin desquamation, sweating, erythema multiforme, dermatitis exfoliative, and Stevens-Johnson syndrome

Urogenital Effects: Abnormal ejaculation (including ejaculation failure, ejaculation disorder, retrograde ejaculation, and decreased ejaculation), decreased libido, priapism, reduced semen volume, urinary tract infection (UTI), dysuria, impotence.

Special Senses: Blurred vision and visual impairment. IFIS has been associated with alpha–1 blocker therapy during cataract surgery.

OVERDOSAGE AND MANAGEMENT

Overdosage of tamsulosin HCl may lead to hypotension. Provide cardiovascular support immediately. Keeping the patient in supine position may help restore blood pressure and normalize heart rate. Consider administration of intravenous fluids if this measure is inadequate. Use vasopressors if necessary and monitor and support renal function as needed. Dialysis is unlikely to be of benefit since tamsulosin is 94% to 99% protein bound.

Tamsulosin's absorption may be impeded by emesis. Gastric lavage, activated charcoal and an osmotic laxative may be useful when large quantities are involved.

Severe headache that resolved on the same day was reported in one patient with an overdose of about 12 mg of tamsulosin HCl. Acute overdose with tamsulosin HCl leading to acute hypotension (systolic blood pressure 70 mmHg), vomiting and diarrhea has been observed at a dose of 5 mg. The patient was given fluid replacement therapy and was discharged on the same day.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE
Store at temperatures not exceeding 25°C.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Tamsulosin HCL (PROZELAX®) 200 mcg Sustained Release Capsule
Blister Foil (Aluminum pouch) by 14's (Box of 28's)

Manufactured by Standard Chem. & Pharm. Co. Ltd.
2nd plant, No. 154, Kai-Yuan Rd., Hsin-Ying, Tainan, Taiwan
Imported and Distributed by UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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Reg. IPOPHIL